

Guidance for Industry and FDA Staff

Guidance for Cardiopulmonary Bypass Oxygenators 510(k) Submissions

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Office of Device Evaluation**

Preface

Public Comment:

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Guidance¹ for Cardiopulmonary Bypass Oxygenator 510(k) Submissions

This guidance document describes a means by which cardiopulmonary bypass oxygenator devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate cardiopulmonary bypass oxygenator device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

1. Device Identification

"Cardiopulmonary bypass oxygenator (21 CFR 870.4350) - A cardiopulmonary bypass oxygenator is a device used to exchange gases between blood and a gaseous environment to satisfy the gas exchange needs of a patient during open-heart surgery." The device is intended for use up to six hours in duration.

2. Purpose and Scope

This guidance document is intended to identify the minimum information to submit in support of a substantial equivalence finding for a cardiopulmonary bypass oxygenator. This guidance includes only oxygenators with integral heat exchangers. It also identifies testing protocols that may be followed in providing the necessary data. Since these protocols may not be applicable to all devices, manufacturers should verify that testing is conducted which provides appropriate data to determine the substantial equivalence of their oxygenator. Manufacturers should be aware that the national and international standards available on oxygenators provide details on characterization and performance testing of these devices, but they do not serve as comprehensive guides for the submission of data necessary for a regulatory review. (ISO 7199:1996(E) and CAN/CSA-Z364.3-M90 (1990))

¹ *This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

3. Definitions

Test oxygenator	the oxygenator submitted for 510 (k) regulatory clearance.
Aged test oxygenator	the test oxygenator after it has undergone appropriate accelerated or real time aging.
Predicate oxygenator	a similar oxygenator to the test oxygenator which has previously been cleared by FDA and is currently in commercial distribution in the United States.
Control blank circuit	a recirculation circuit that does not include an oxygenator but is otherwise identical to those circuits used to test oxygenators for blood damage.
Static control blood	a small volume of blood that is not circulated in a circuit and used to monitor autohemolysis.
Index of Hemolysis	the mass of hemoglobin released from the red blood cells per 100L of blood pumped through the device.
Modified Index of Hemolysis	the ratio of the amount of hemoglobin released into the plasma normalized by the total amount of hemoglobin pumped through the device.

4. Oxygenator Testing

To evaluate substantial equivalence of a cardiopulmonary bypass oxygenator, provide data addressing the biological, material, physical, and performance characteristics over the expected storage (shelf life) and use lifetime of the oxygenator. The potential failure modes for oxygenators, which should be investigated thoroughly, include leaks, toxicity, loss of gas transfer efficiency, gas embolism, thromboembolism, and blood damage. The oxygenator should be tested over its entire performance specification range under expected use conditions for six hours in duration. *In vitro* testing should be conducted according to an established protocol using at least five devices for each test. Submit the testing protocols along with the results of the tests reported in a statistically meaningful manner. Include the range of values, mean, standard deviation and standard error of the mean for each data set. For any comparative test, provide the p-value or similar measure indicating statistical significance of the comparison. Calibrate all instruments and equipment used in conducting these tests, to minimize the limit of testing error. Accuracy of the test apparatus should conform to that in section 11.1.2 of standard CAN/CSA-Z 364.3M90 (1990).

4.1 *Comparative Data*

For all testing, the test oxygenator should be compared to a similar currently legally marketed oxygenator, the predicate.

4.2 *Preparation of the Test Oxygenator*

Parallel testing should also be performed on the oxygenators only after they have undergone appropriate accelerated or real time aging and sterilization. The purpose of the testing is to determine adverse effects that may not be apparent in recently manufactured devices.

Before testing the test oxygenator subject it to shock/vibration and temperature/humidity conditioning to simulate the expected use environment and anticipated transport, and storage conditions. The oxygenator can be tested in accordance with tests that best simulate the device's exposure, including the shocks, vibrations, temperatures and humidity expected prior to and during intended use. Following environmental testing, the device should be visually inspected and functionally tested. Any evidence of damage or inability to perform within specification will constitute a failure of the test. Some recommended standards for environmental testing are IEC 68-2 Basic Environmental Test Procedures, MIL-STD-810E, UL-2601.

4.3 *Biological Compatibility*

The materials of the finished oxygenator should be tested for biocompatibility, e.g., cytotoxicity, irritation or intracutaneous reactivity, systemic toxicity, and hemocompatibility, in accordance with ISO 10993 (Biological Evaluation of Medical Devices) and sensitivity and genotoxicity in accordance with FDA Blue Book Memo G95-1: Use of International Standard ISO 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" dated May 1, 1995. The materials of the finished oxygenator should be compatible with any compounds expected to be introduced into the blood circuit and exposed to the oxygenator (e.g., anesthetic agents, other gases, liquids, and medications).

4.4 *Physical Characterization/ Integrity*

The mechanical integrity of the finished, sterilized, and aged oxygenator should be demonstrated by subjecting the blood, water (within integral heat exchangers), and

gas pathways to pressures and flow rates of at least 1.5 times the recommended maximum operating limit for 6 hours.

4.4.1 Blood Pathway Integrity

Using water as the test liquid, subject the blood path of the device to 1.5 times the maximum recommended pressure for 6 hours to determine whether leakage occurs, i.e., blood side to gas side, blood side to atmosphere. The pressure should be increased gradually to avoid water hammer or shock waves.

4.4.2 Heat Exchanger Fluid Pathway Integrity

Using water as the test liquid, subject the heat exchanger fluid path of the device to 1.5 times the maximum recommended pressure for 6 hours to determine whether water leakage occurs, i.e., water side to blood side, water side to atmosphere.

4.4.3 Gas Pathway Integrity

Subject the gas pathway of the device to 1.5 times the maximum recommended pressure limit for 6 hours to determine whether there is loss of mechanical integrity of the connectors, housing, or integral structures.

4.4.4 Blood Volume Capacity of Oxygenator

Determine the static and dynamic volumes of blood within the device over the entire range of operating conditions. The static priming volume is the minimum volume of fluid residing in the oxygenator after priming at zero flow.

4.5 Performance Characterization

The performance characterization of the aged test, and predicate oxygenators should be based on dynamic testing over the entire range of operating variables for the aged, sterilized test and predicate oxygenator for six hours in duration using whole blood. Submit testing protocols with detailed descriptions and figures of the testing circuit components. Submit data in tabular and graphical forms. Both testing protocols and

data should be submitted on oxygen and carbon dioxide transfer rates, blood side pressure drop, heat exchanger performance, and blood cell damage. Atmospheric pressure during testing should be noted in the submission.

4.5.1 Blood Used for Evaluations

Use fresh whole animal blood collected and stored at 5°C for less than 24 hours for performance testing . Although bovine blood is most commonly used, sheep, goat or pig blood may also be used. To minimize the effects of interanimal variation, it is advised that the common blood pool be composed of blood from more than one animal. FDA recommends anticoagulant concentration of 4500 units of heparin per liter of blood. If blood is stored for more than 24 hours, use antibiotics.

4.5.2 Oxygen and Carbon Dioxide Transfer Rates/ Blood Side Pressure Drop/Plasma Leakage

The oxygenator's gas transfer characteristics, blood side pressure drop, and plasma leakage are evaluated using operational variable settings that span the manufacturer's recommended operating range of six hours.

4.5.2.1 General Testing

Identify the components of the testing circuit (described in the text and in figures) and include the following components as a minimum:

- Test oxygenator
- Conduit tubing
- Connectors
- Blood pump
- Blood reservoir
- Separate oxygenator acting as a "deoxygenator"
- Heater/cooler unit
- Monitors and, or transducers

For determining gas transfer rates, a separate oxygenator is used in the loop to deoxygenate the blood and maintain the same venous

inlet blood conditions to the oxygenators under evaluation. Blood sampling ports directly before the inlets and directly after the outlets of each of the oxygenators are used to measure blood gases and pressure drops across the oxygenators as a function of the operating variables.

4.5.2.2 Inlet Blood Conditions to Each Oxygenator for Gas Transfer

The testing circuit for evaluating gas transfer should provide an identical blood condition at the inlet of each oxygenator as described. This should be checked at baseline, 90,180,270 and 360 minutes.

- Hemoglobin concentration: 12 ± 1 g/dl
- Oxyhemoglobin saturation: $65 \pm 5\%$
- $p\text{CO}_2$: 45 ± 5 mm Hg
- Base excess: 0 ± 5 mmol/L
- Temperature: $37 \pm 2^\circ\text{C}$
- pH: 7.4 ± 0.1

Since the characteristics of blood may degrade over time outside the body, the gas exchange capability of the oxygenator may be compromised. Therefore, to effectively assess the gas exchange capability of the oxygenator, circulating blood may be replaced with fresh blood after three hours of recirculation. Obtain a blood sample immediately after the blood exchange to verify that inlet blood conditions specified above are met.

4.5.2.3 Gas Transfer and Blood Pressure Drop Data Over the Operational Range of the Oxygenator

For gas exchange and blood side pressure drop measurements, cover the manufacturer's range of specified blood flow (i.e., minimum, nominal, and maximum recommended blood flows) for 6 hours duration. At each blood flow rate, record the gas transfer (refer to Tables 1, 2, and 3) for various gas flow rates within the manufacturer's recommended range. Data should be included for gas to blood flow rate ratios of 0.5:1, 1:1, and 2:1. The composition

of the sweep gas and the gas pressures should also be provided at the gas inlet and outlet ports for each setting. The sweep gas and the gas pressures need to be met and corrected throughout the testing period.

TABLE 1. Oxygen Gas Transfer Data Set *

Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum) per the manufacturer's recommendation, and according to the labeling. FDA suggests the table format given below.

Gas: Blood Flow Rates (L/min)			
Minimum Blood Flow Rate = (L/min)	F/Q = 0.5:1 Minimum	F/Q=1:1 Moderate	F/Q=2:1 Maximum
Inlet PO ₂ , % Sat, pCO ₂ , pH			
Outlet PO ₂ , % Sat, pCO ₂ , pH			
Calculate Oxygen Transfer Rate ⁺			

⁺ Oxygen Transfer Rate [ml O₂ (STPD)/min] = Q x (CaO₂ outlet - CvO₂ inlet)

Q = blood flow rate in L/min.

F = gas flow rate in L/min.

CaO₂ outlet = blood O₂ content (ml O₂/L blood) calculated at the outlet

CvO₂ inlet = blood O₂ content (ml O₂/L blood) calculated at the inlet

Since CaO₂ or CvO₂ = CaO₂ (or CvO₂) bound to hemoglobin + CaO₂ or CvO₂ dissolved in the plasma, CaO₂ outlet and CaO₂ inlet can be calculated from the following formula (assuming that the total hemoglobin concentration of the blood is 12 g/dl):

CvO₂ (or CaO₂) [ml O₂/L blood] = 12 g Hb/ 100 ml blood x 1.34 ml O₂/ 1 Gm Hb x 1000 ml blood/ 1 L blood x (% O₂ saturation) + (PO₂ mmHg x 0.00314 ml O₂/ (100 ml blood) (mmHg) x 1000 ml blood/ 1 L blood)

STPD = standard temperature and pressure, dry

TABLE 2. Carbon Dioxide Gas Transfer Data Set *

* Provide a table with data for each of the three different blood flow rates (min, max, and nominal). FDA suggests the table format given below.

Blood Flow Rate = (L/min)	Gas Flow Rates (L/min)		
	F/Q = 0.5:1 Minimum	F/Q = 1:1 Nominal	F/Q = 2:1 Maximum
Inlet gas composition			
Outlet gas composition			
% Δ CO ₂ [ml CO ₂ (STPD)/L gas]			
Calculate CO ₂ Transfer Rate ⁺			

The gas streams entering and leaving the oxygenator should be analyzed for CO₂. The CO₂ transfer rate is calculated as follows:

$$^+ \text{ CO}_2 \text{ Transfer Rate [ml CO}_2 \text{ (STPD)/min]} = F \times \% \Delta \text{CO}_2$$

F = gas flow rate, exiting the blood-gas exchange device, L/min.

% Δ CO₂= the change in carbon dioxide concentration between the inlet and outlet streams [ml CO₂ (STPD)/L gas].

TABLE 3. Blood Pressure Drop Data Set *

* Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum). Hydrostatic differences between the locations of the inlet and outlet pressure transducers should be accounted for in the table. FDA suggests the table format given below.

Blood Flow Rate = (L/min)	Minimum	Nominal	Maximum
Inlet Blood Pressure (mmHg)			
Outlet Blood Pressure (mmHg)			
Blood Pressure Drop (mmHg)			

Provide a graph along with the above tables showing gas transfer rate (O_2 and $C O_2$) as a function of blood flow rate and gas flow rate. Determine the blood flow rate at which the gas exchange is sufficient to cause the outlet O_2 saturation to be 95% O_2 saturation.

Provide a graph along with the above data tables showing the blood side pressure drop as a function of blood flow rate.

To better simulate the clinical use of the device, submit data that shows the effects on gas transfer and pressure drop when the blood side outlet of the oxygenator experiences a backpressure of approximately 100 mmHg during use.

4.5.2.4 Gas Transfer, Pressure Drop, and Plasma Leakage Data

In addition to recording pressure drops and gas exchange parameters as stated above, monitor plasma leakage over a six-hour period.

During the testing, blood should be circulated at the maximum recommended flow rate. The specified time intervals for tabular and graphical data are at 10 min, 1 hr, 2 hr, 4 hr, and 6 hr.

5. Heat Exchanger Performance Evaluation

The performance of the oxygenator's heat exchanger is evaluated using fixed temperature differences between the inlet blood and water, fixed water flow rates, and blood flow rates spanning the recommended operating range specified by the manufacturer.

5.1 *General Testing*

Identify the components of the testing circuit (described in the text and in figures) and include the following components as a minimum:

- Test oxygenator
- Conduit tubing
- Connectors
- Blood pump
- Blood reservoir
- Separate heat exchanger acting to chill the blood
- Monitors and, or transducers

For determining the performance factor of the oxygenator's heat exchanger, a separate heat-exchanging device is used in the loop to maintain the same venous inlet blood temperature conditions to each of the oxygenators under evaluation. Blood sampling ports directly before the inlets and directly after the outlets of each of the heat exchangers are used to measure the blood temperature as a function of the operating variables.

5.1.1 **Inlet Blood Conditions to Each Oxygenator**

The blood should have total hemoglobin content of 12 ± 1 g/dl. The inlet blood temperature to each oxygenator should be maintained at 30 ± 1 °C using a water bath. The inlet water temperature to each oxygenator should be maintained at 40 ± 1 °C using a water bath.

5.1.2 Heat Transfer and Water Pressure Drop Data over the Operational Range of the Oxygenator

For heat exchange measurements, cover the manufacturer's range of specified blood flow rates (i.e., minimum, nominal, and maximum recommended blood flows). At each blood flow rate, record the temperature needed to determine heat transfer (refer to Tables 4 and 5) for various water flow rates within the manufacturer's recommended range.

5.1.3 Heat Transfer and Water Pressure Drop Data (Six hour duration)

Monitor the heat exchange and waterside pressure drop over a six-hour period, in addition to recording blood and water parameters as stated above. During the testing, blood should be circulated at the maximum recommended flow rate. The specified time intervals for tabular and graphical data are at 10 min, 1 hr, 2 hr, 4 hr, and 6 hr.

TABLE 4. Heat Exchanger Data Set *

* Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum). FDA suggests the table format given below.

Water Flow Rates (L/min)			
Blood Flow Rate = (L/min)	Minimum	Nominal	Maximum
Inlet Blood Temperature (°C)			
Outlet Blood Temperature (°C)			
Inlet Water Temperature (°C)			
Outlet Water Temperature (°C)			
Calculate Performance Factor ⁺			

⁺ The efficiency of the heat exchanger can be expressed as a heat exchanger performance factor (R) defined as the difference between the outlet and inlet oxygenator blood temperatures divided

by the difference in temperatures in °C between the water and blood at their respective inlets to the oxygenator.

$$R = (B_o - B_i) / (W_i - B_i)$$

Where B_o = blood temperature at the oxygenator outlet
 B_i = blood temperature at the oxygenator inlet
 W_i = water temperature at the oxygenator inlet

TABLE 5. Water Pressure Drop Data Set *

* Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum). Hydrostatic differences between the locations of the inlet and outlet pressure transducers should be accounted for in the table. FDA suggests the table format given below.

Water Flow Rates (L/min)			
Blood Flow Rate = (L/min)	Minimum	Nominal	Maximum
Inlet Water Pressure (mmHg)			
Outlet Water Pressure (mmHg)			
Water Pressure Drop (mmHg)			

Provide a graph along with the above data tables showing the heat exchanger performance factor as a function of both blood flow rate and water flow rate. Provide a graph along with the data tables showing the waterside pressure drop as a function of blood flow rate and water flow rate.

To better simulate the clinical use of the device, data may also be submitted showing the effects on heat transfer and water pressure drop when the blood side outlet of the oxygenator experiences a backpressure of approximately 100 mmHg during use.

5.2 Blood Damage Performance Evaluation

The oxygenator will be evaluated for in vitro blood damage by monitoring the plasma hemoglobin concentration, WBC and platelets for six hours in duration.

5.2.1 General Testing

Identify the components of the testing circuit (described in the text and in figures) and include the following components as a minimum:

- Test oxygenator
- Conduit tubing
- Connectors
- Blood pump
- Blood reservoir
- Heater/cooler unit
- Monitors and, or transducers

Also submit data for the aged, sterilized test oxygenator and the predicate oxygenator placed in identical testing circuits using the same blood source. Evaluate a "control blank circuit" to determine how much damage is caused by the components of the recirculation circuit when an oxygenator is not present.

5.2.1.1 *Condition of Blood for Damage Testing*

- Hemoglobin concentration: 12 ± 1 g/dl
- $p\text{CO}_2$: 40 ± 5 mm Hg
- pH: 7.4 ± 0.1
- Temperature: $37 \pm 2^\circ\text{C}$

5.2.1.2 Blood Damage Testing Protocol

A detailed protocol with figures for performing the blood damage testing should be provided. The blood flow rate and the gas flow rate to the oxygenator will both be the maximum specified by the manufacturer. The back pressure on each oxygenator should be maintained at approximately 100 mmHg to simulate clinical use conditions. Important procedures to control include:

- precise occlusivity setting of the roller pumps prior to blood introduction in every test loop
- priming and wetting of all surfaces of the circuits by recirculating saline through the circuits for 5 min. prior to the introduction of blood
- minimizing any air/ blood interfaces, minimizing the total circuit blood volume, and
- clearing each blood sampling port by withdrawing (for disposal) approximately 1 ml of blood prior to taking the actual blood sample using a separate syringe

Inherent in this type of testing is the assumption that the blood damage caused by the other (non-oxygenator) components of the testing circuits is identical in each circuit. Experience has shown that this is not necessarily true and that precise occlusivity setting of the roller pumps using saline prior to the introduction of blood is an important step in the testing. Due to uncontrollable variations in blood, it is preferable to perform the blood damage testing on the test oxygenator circuit, the aged, sterilized test oxygenator circuit, the predicate oxygenator circuit, and the control blank circuit at the same time using the same blood pool. However, this may not always be possible. The day, time, and blood pool that were used in the testing of each circuit should be apparent in the final report. The total volume of blood in the test circuits should be identical and minimized so that the sensitivity of the testing for

blood damage is increased. In general, the total circuit blood volume should be 500 - 2500 ml depending on the maximum recommended blood flow rate.

5.2.1.3 *Blood Damage Data Reporting*

For *in vitro* blood damage testing, provide data according to the sampling schedule in Table 6. Raw data and corrected data (with respect to "baseline" values) for each of the individual testing circuits should be provided in both tabular and graphical form. The plasma hemoglobin is reported as a concentration (mg/dl) that increases over time. Mean (\pm SD) results should also be tabulated and graphed for the test oxygenator circuit, - omit and the predicate oxygenator circuit, the aged, sterilized test oxygenator circuit and the control blank circuit. The day, time, and blood pool that were used in the testing of each circuit should be apparent in the final report. Appropriate statistical testing should be performed to account for testing using different blood source pools at different times.

TABLE 6. Parameter Sampling Schedule

Parameter	Sampling Schedule (minutes)							
	Main Blood Pool	Baseline*	10	30	90	180	270	360
Plasma Hemoglobin Concentration	X	X	X	X	X	X	X	X
Activated Clotting Time (ACT)	X	X				X		X
Hematocrit	X	X		X		X		X
Total Blood Hemoglobin	X	X		X		X		X
Temperature		X	X	X	X	X	X	X
Blood Gas Values (pO ₂ , pCO ₂ , pH _i)		X	X	X	X	X	X	X
Blood and Gas Flow Rates		X	X	X	X	X	X	X

* "Baseline" refers to the time (at "zero minutes" on the sampling schedule) after all of the blood has been introduced into the circuit, all bubbles have been removed from the circuit, the recirculation pump has been run at the proper blood flow rate for at least 5 minutes to insure complete mixing throughout the circuit, and the blood gas values, gas flow rate, and gas composition conditions have been established.

A traditional normalized "index of hemolysis" (IH), interpreted as the mg of hemoglobin released from the red blood cells per 100L of blood pumped through the device, should be calculated using the following formula (be sure to check the units of each entity in the equation):

$$IH [mg/100L] = [(\Delta \text{plHgb}/\Delta t) \times ((100 - \text{Hct})/100) \times \text{Vol.} \times 1000] / Q$$

$\Delta \text{plHgb}/\Delta t$ (mg/dl min) = the slope of the plasma hemoglobin concentration (mg/dl) versus time (min.) plot obtained from a linear best-fit to this data.

Hct (%) = average hematocrit of the blood circuit.

Vol (L) = average blood volume of the circuit.

Q (L/min) = blood flow rate during testing.

Traditionally, only the plasma hemoglobin concentration at time zero and time 360 min were used to calculate the IH. However, using the slope of the plasma hemoglobin concentration versus time plot allows all of the data to be equally weighted in the determination of the IH. Although the IH has been used by several groups to "normalize" their blood damage data, it actually varies directly with the hematocrit. For this reason, the "modified index of hemolysis" (MIH), which is the ratio of the amount of hemoglobin released into the plasma normalized by the total amount of hemoglobin pumped through the device, should also be calculated in the submission as follows:

$$\text{MIH [mg/ mg]} = [(\Delta\text{pHgb}/\Delta t) \times ((100 - \text{Hct})/100) \times \text{Vol} \times 10^6] / (Q \times \text{Hb})$$

Where Hb (mg/dl) = average total hemoglobin concentration in the circuit.

Although a standardized testing protocol has not been established, supplemental testing for up to six hours in duration at the manufacturer's specified minimum blood flow rate (with blood with an ACT of 300-450 seconds and a normal to high platelet count) is also recommended. In-line monitoring for microparticle formation and post-test oxygenator evaluation for evidence of areas of blood stasis, thrombus deposition, and maldistribution of flow are encouraged.

5.3 *Acceptable Endpoints*

The oxygenator should not fail any of the testing after undergoing shock, vibration, temperature, and humidity conditioning.

5.4 *Biological/ Material Compatibility*

The test oxygenator will not be significantly different than the predicate oxygenator in terms of its biological or material compatibility.

5.5 *Physical Characterization/ Integrity*

The test oxygenator should withstand 1.5 times maximum recommended flow rates (gas, blood, and water) and pressures.

5.6 Performance Characterization

- Mean oxygenator outlet saturation should be 95% at each designated blood flow rate during each test period. CO₂ elimination should be at least 80% of O₂ delivery.
- The oxygen and carbon dioxide transfer rates should not vary by more than \pm 15% of the initial test values over the entire six-hour test period.
- The blood side pressure drop across the device should not exceed 400 mmHg.
- Plasma leakage (the volume of fluid collected from the device gas outlet each hour) should be < 5cc/hr in any test period.

6. Packaging

6.1 Performance Evaluation

- Perform a sterilization validation to ensure that the sterilization process is capable of providing the Sterility Assurance Limit (SAL) of 10⁻⁶, in accordance with suitable guidance (e.g., ANSI/AAMI VP20-1994, Section 4.5 (Sterility), ANSI/AAMI/ISO 11134-1993, ANSI, AAMI/ISO 11135-1994, and ANSI/AAMI/ISO 11137-1994). Alternate sterilization methods should be validated to an appropriate SAL.
- Describe the sterilization method that will be used; the method that used to validate the sterilization cycle, and the SAL.
- Describe how the packaging serves to maintain the device sterility. For ETO sterilization, state the maximum levels of residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol. State whether the product is non-pyrogenic, and describe the method used to make that determination. For radiation sterilization; state the radiation dose used. See also, Sterility Review Guidance, and Revision of 11/18/90 #K90-1.
- Conduct preclinical and/or clinical (in vivo) evaluations of devices incorporating new or substantially modified materials or design, in accordance

with ANSI/AAMI VP20-1994, Section 6 (Requirements for In Vivo Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through in vitro testing.

6.2 Labeling -- Instructions For Use

- Provide a statement that biological testing (including pyrogen and bioburden testing) will be or has been performed to assess acceptable limits of biological contaminants.
- Provide a statement that package shelf life validation (including package integrity/distribution testing, accelerated aging, microbial challenge testing, and real time follow-up) will be or has been performed, in accordance with ANSI/AAMI VP20-1994, Section 4.5.1 (Shelf life), to determine that the device and package will maintain their integrity for the period of time specified on the device label, or provide a justification as to why such validation is not necessary.
- Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).
- State that the product is supplied sterile on the product package label and in the Instructions for Use.
- Provide instructions for opening the sterile package.
- Instruct the user that sterility cannot be assured if the packaging has been opened or damaged.
- State that the health care provider must observe aseptic technique in preparation and use of the device.